Lecture: Endocrine Physiology

The endocrine system is a chemical control system. It functions in conjunction with the nervous system to control the internal environment (homeostasis).

I. Endocrine Glands

A. Glands without ducts

1. Secrete HORMONES ("to set in motion") into the intercellular spaces and they pass directly into the blood and is then distributed to all parts of the body via the circulatory system.

2. Hormones - chemical secretions of the endocrine glands.
   a. chemical types -
      1). proteins and polypeptides (endodermal origin)
      2). Amines (endodermal origin)
      3). steroid (mesodermal origin)

3. Hormones - act to maintain homeostasis by altering cellular activity.
4. Hormones can affect

   a. organ or groups of organs directly ("target organ(s)")
   b. other endocrine glands called "target glands"
      [these hormones are called tropic hormones]

B. Nervous System vs. Endocrine System

	Nervous System	Endocrine System
Effects	rapid & short-lasting	slower & longer lasting
Controls	muscles & glands	activities of cells:
		a. metabolism
		b. reproduction
		c. stress responses
		d. fluid-electrolyte balance
		e. acid-base balance
		f. energy balance

II. Pituitary Gland - (Hypophysis) [Master Gland]

A. Location

1. in Sella Turcica of sphenoid bone
2. attached to Hypothalamus by a stalk called Infundibulum

B. Structure

1. Anterior lobe – [glandular part] - Adenohypophysis
2. Posterior lobe – [neural part] – Neurohypophysis

C. Anterior Pituitary - (Adenohypophysis)

1. Hormone secretions controlled by secretions from the hypothalamus produced by nerve cells and control the release of hormones by Endocrine glands; these hormones are called releasing factor

Growth Hormone (GH) - Somatotrophic Hormone (STH)

1. Increases Growth and Maintenance of Organs by:

   a. stimulating protein anabolism
   b. promotes fat catabolism (use of fat rather than sugars for energy)

2. Abnormal Secretions of STH

   a. Giantism – hypersecretion during childhood (before epiphyseal plates close)
   b. Acromegaly – hypersecretion during adulthood
   c. Dwarfism – hyposecretion during childhood
   d. Cachexia (Simmond's Disease) - hyposecretion during adulthood causes premature aging and atrophy of organs

Prolactin - (Lactogenic Hormone)

1. promotes breast development during pregnancy
2. stimulates mammary glands to produce milk after delivery

Thyriod Stimulating Hormone (TSH) - (Thyrotropin)

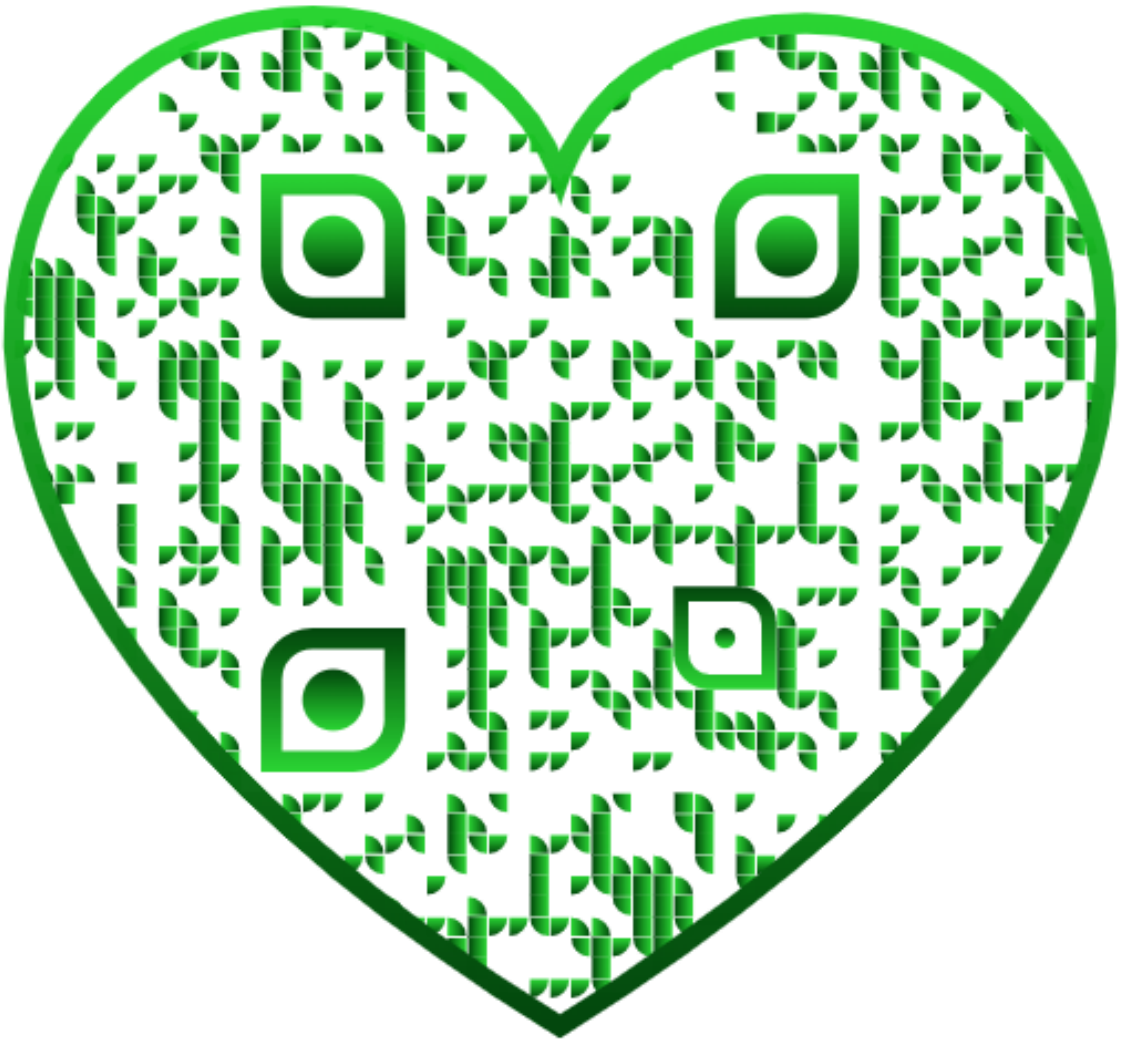
1. promotes growth of the Thyroid Gland
2. stimulates the secretion of the Thyroid Hormone

Adrenocorticotropin – (ACTH)

1. promotes growth of the Adrenal Cortex
2. stimulates the secretion of Cortical Hormones
3. stimulates Fat Catabolism & Glycogenesis

Gonadotropins - FSH and LH

1. Follicle Stimulating Hormone (FSH)
   a. female - stimulates the Ovarian Follicles to Develop and produce ova
      - stimulates the Ovarian Follicles to secrete Estrogens
   b. male - stimulates the production of sperm
      - stimulates the secretion of Testosterone



2. Luteinizing Hormone (LH)
   a. female - associated with FSH in development of the Ovarian Follicles
      - stimulates development of the Corpus Luteum following ovulation
      - stimulates Corpus Luteum to secrete Progesterone
   b. male - stimulates the Interstitial Cells to secrete Testosterone
      (also called Interstitial Cell Stimulating Hormone [ICSH])

D. Posterior Pituitary Lobe (Neurohypophysis)

1. Antidiuretic Hormone (ADH) - produced in the hypothalamus and collected and secreted by the posterior lobe

   a. increases the permeability of the kidney tubules to water
   b. promotes the reabsorption of the water from the urinary filtrate resulting in a smaller volume of urine
   c. Diabetes insipidus - condition resulting in larger volumes of urine produced - may be treated with vasopressin

2. Oxytocin

   a. stimulates powerful contractions of the pregnant uterus at the time of delivery
   b. causes milk ejection from the lactating breast

III. THYROID GLAND

A. Location - lower aspect of larynx and upper trachea
   - two lateral lobe connected by an isthmus on anterior surface of superior trachea

B. Histology & Physiology

1. Thyroid Follicles - functional units
   a. follicle cells secrete Thyroxine (Thyroid Hormone)
      Thyroxine is a combination of Tyrosine & Iodine to make two compounds:
      Tetraiodothyronine - T_4
      Triiodothyronine - T_3

Thyroxine is transported in the blood as Thyroid-binding Globulin (TBG)

2. Test for Thyroid Activity -
   - thyroxine is transported in combination with plasma proteins
   - (TBG) - PBI test (protein Bound Iodine) serves to quantify the levels of thyroxine in the blood

3. thyroxine Action -

   a. Calorigenic Effects - increases Catabolism and produces extra body heat
      1 mg of thyroxine = an increased heat production of 1000 calories

   b. Growth & Development - Works with STH to produce growth and development of tissues and organs
      - Nervous Tissue particularly affected
      - hyposecretion results in Mental Retardation

4. Metabolic Effects -

   a. diuretic
   b. protein and carbohydrate catabolism (stimulates cellular uptake)
   c. increases activity of nervous system
   d. increases heart rate
   e. causes muscular weakness

5. Parafollicular Cells - secrete Thyrocalcitonin (TCT)

   a. decreases excretion of Calcium & Phosphate ions
   b. increases Osteoblast activity - Ca^{+2} & PO^{-3} deposition in bone

6. Disorders of the Thyroid

   a. Hyperthyroidism (Grave's disease)

   - elevated PBI
   - increases nervousness and irritability
   - elevated BMR
   - exophthalmos - results in edema behind the eyes

   b. Hypothyroidism

Cretinism - occurs if the hyposecretion is during fetal or early developmental life.
   - results in reduced metabolism
   - results in reduced growth
   - results in mental retardation

Myxedema - occurs if the hyposecretion is during adult life
   - results in reduced metabolism
   - results in reduced mental & physical activity
   - results in increased blood pressure
   - results in accumulation of subcutaneous fluids

IV. Parathyroids

A. Location - 4 or 5 small round bodies on the posterior surface of the lateral lobe of the thyroid gland

B. Function - secretes the Parathyroid hormone that controls Blood Calcium homeostasis

   1. increases Ca^{+2} and Mg^{+2} absorption from the Intestines, Kidneys and Bones [raises

blood calcium levels]

2. Increases PO^{-3} excretion [lowers blood phosphate levels]

C. Disorders of parathyroid activity

1. Hypocalcemia - causes by hyposecretion of PTH
-results in Tetany [muscle spasms and convulsions]

2. Hypercalcemia - causes by hypersecretion of PTH
-results in a fibrous bone disease [osteitis fibrosa cystica or also called Von Recklinghausen's Disease of the bone]

VI. Adrenal Glands

A. Location - consists as two triangular glands and each sit like a cap on the kidneys

B. Adrenal Cortex - secretes the Adrenal Cortical Hormones

1. Glucocorticoids produced by cells of the Zona Fasciculata

a. corticosterone
b. cortisol (hydrocortisone)
c. cortisone
- elevates blood sugar levels by acceleration of glycogenolysis and gluconeogenesis - [causes conversion of proteins into carbohydrates - resulting in "Tissue Wasting"]
- promotes protein catabolism
- promotes fat catabolism
- promotes vasoconstriction to maintains normal blood pressure
- promotes stress resistance through Anti-Inflammatory actions

2. Mineralocorticoids - produced by the cells of the Zona Glomerrulosa

a. aldosterone
- causes Sodium retention and Potassium excretion
- causes water retention and blood pressure increases

3. Gonadocorticoids - produced by cells of the Zona Reticularis

a. these are the sex hormones that are produced by the adrenal cortex in small amounts in both males and females

4. Abnormal Adrenal Cortical Function:

a. Addison's Disease - caused by Hyposecretion of Cortical hormones
- results in increased blood potassium levels
- results decreased sodium retention and dehydration

- results decreased blood glucose levels
- results decreased blood pressure
- results decreased stress resistance
- results increased risk of kidney failure

b. Cushing's syndrome - caused by Hypersecretion of Cortical Hormones.
- results in shifts of the body fat to the face and shoulders
- results in general body weakness
- results in altered carbohydrate & electrolyte metabolism

c. Adrenogenital Syndrome - caused by Hypersecretion of Gonadotropins
- results in premature sexual development in both males and females
- results in masculinization of females

C. Adrenal Medulla Hormones - Epinephrine & Norepinephrine

Effects: - Sympathomimetic
- Increased blood pressure due to increased heart rate & constriction of blood vessels
- Increased respiratory rate and dilation of bronchioles
- Increased blood sugar and cellular metabolism
- Decreased digestive tract activity

VII. Pancreas - (Islets of Langerhans cells)

A. Hormones

1. Insulin - secreted by the Beta Cells
- promotes lower blood glucose levels by:
- promoting glycogenesis, protein synthesis, and lipogenesis
- promoting cellular uptake

2. Glucagon - secreted by the Alpha Cells
- promotes higher blood glucose by:
- promoting glycogenolysis

Diabetes mellitus (DM)

Normal blood sugar level

1. The fasting blood sugar level at health is between 70 -110mg%. but only when the fasting level is >140mg% then, according to WHO, the person is diabetic. The intermediate zone, i.e. between 111 to 139mg% is IGF (impaired fasting glucose) level. The IGF are not absolutely healthy.
2. The post prandial (pp) (2hrs of the 75 gm glucose meal) blood sugar level, at health is < 140mg%. but according to WHO, the pp blood sugar level in diabetic has to be >200mg%. the intermediate zone, viz, 141-199mg%, has thus impaired glucose tolerance test.

Diabetes mellitus (DM): DM (honeyed urine) is characterized by hyperglycemia. If left with or inadequate treatment, the victim tends to die prematurely.

Cut off level for hyper glycemia

1. Normal fasting level a blood glucose is maximum, up to 6.1 m mole/L(=110mg/100ml).
2. PP (post meal), up to 8.9m mole /L(=160mg/100ml).

According to WHO, a person is diabetic, if his /her plasma blood glucose level is (i) fasting > 7.8 mole/L (=140mg/100ml) and/or (ii) PP >111m mole/L (=200mg/ 100ml)

Features of DM

Classical features are: (i) polyuria (ii) polydypsia excessive drinking (iii) polyphagia (excess eating) (iv) wasting.

Polyuria: hyper glycemia exceeding renal threshold results in glucosuria → sugar molecules in the renal tubules increase the osmolarity of tubular fluid and acts as osmotic diuretic → diuresis =→ polyuria.

Polydypsia: polyuria results in water loss, dehydration → thirst develops → polydypsia.

Polyphagia: Glucose is being lost via urine → this causes a demand of more fuel in the body → polyphagia.

Wasting – To meet the challenge of rising demands of fuel, endogenous proteins (muscle proteins) are catabolized → substrates for gluconeogenesis produced no doubt but this also causes loss of the mass of the muscles → wasting.

Long term complications of DM

I. Big blood vessels

As a long term complication of DM, atherosclerosis is foremost. Atterosclerosis is very common even in the non-diabetics, but the disease is particularly common in the diabetics.

Causes:

1. In diabetics for various reasons, serum cholesterol and LDL tend to be high → proneness to develop atherosclerosis increases.
2. LDL molecules (which carry most of the cholesterol inplasma) in DM, are oxidized and glycosylated. Such molecules are deposited in subintimal layers of big vessels causing atherosclerosis.

As a result of such atherosclerosis, diabetics are particularly prone to such clinical conditions like angina pectoris/myocardial infarction / cerebro vascular accidents, etc.

II. Microangiopathy

In this condition capillary is thickened → leading to obliteration of blood flow through the affected capillaries → anoxic damage of the tissue supplied by these capillaries. Cause of thickening is not clear. One fact is, prolonged hyperglycemia leads to formation of sorbitol (an oxidized product of glucose) in the blood → this sorbitol in some way causes the capillary thickening.

When (i) renal arterial capillaries develop microangiopathy, the clinical condition is diabetic nephropathy, (ii) when retinal vessels are affected, it is diabetic retinopathy.

AGE

In long standing hyperglycemia, glucose molecules are conjugated with various proteins (eg. Hb or albumin). Such conjugation occurs either by "glycosylation" or by "glycation". "Advanced glycosylated/glycated end products" or "AGE" development facilitates atherosclerosis development. Therefore it is a sound policy to estimate glycosylated Hb or plasma albumin to asses the damage done by DM.

III. Neuropathy

In this condition nerve fibers degenerate. ANS or somatic or both varieties of nerves can be damaged. Accordingly there can be impotence /incontinence /gastroparesis/ constipation (ANS damage) or loss of tendon reflexes /weakness of skeletal muscles etc. Brain is not affected.

DKA

DKA is a diabetic keto acidosis and is a medical emergency.

Pathogenesis: Lack of insulin leads to unsatisfactory combustion of glucose → therefore, to meet the demands of fuel there is excessive adipose tissue lipolysis. Also lack of insulin causes (by withdrawing the inhibitory effect on adipose tissue lipase) stepped up lipolysis.

As a result, massive amounts of FFA become available after β oxidation in liver, this leads to massive amounts of acetyl co A (=2c molecules) formation. These 2C molecules conjugate to produce 4C molecules /structures (like aceto acetic acid/β hydroxyl butyric acid) and a 3C structures (in the urinary bladder) viz, acetone.

i. Acetoacetic acid
ii. Hydroxyl butyric acid and

iii. Acetone are collectively known as "ketone bodies" and

Cause:

- lowering of blood pH and
- hyper osmolality of plasma

} both are lethal conditions

Classification of hyperglycemic conditions

Chronic hyperglycemia can be due to (i) primary causes, or (ii) secondary causes. Secondary causes are due to such diseases like (i) pancreatic injury (cancer /pancreactomy) (iii) Cushing's syndrome etc. Primary cause of chronic hyper glycemia is DM.

Subclasses of DM are: I. IDDM, and II. NIDDM.

- **Type I** -IDDM (insulin dependent DM) cases are those where there is no β cell and endogenous insulin is absent. This is because of β cells are destroyed by some disease (say autoimmune disease following a viral infection). IDDM cases usually develop while the patient is still young (hence in the past it was known as "juvenile diabetes") and they must be treated with insulin, otherwise they die.
- **Typeii** - NIDDM (non insulin dependent diabetes mellitus). Here the victims are usually middle aged, often obese and physically underactive, and have a +ve family history of DM. Here the insulin secretion is alright, also the receptors in the target cell are present but there is some fault beyond the receptor. That is, the receptor insulin complex formation occurs as usual but after that further events (=the "transduction of signal") in the target cell are faulty → the biological effects do not develop.

  NIDDM cases may be treated with insulin but instead of insulin they can be treated with oral hypoglycemic agents also. Indeed many NIDDM can be treated by non pharmacological measures alone (ie, without drug). Most cases of DM are of NIDDM-variety.

Hypoglycemia

This is a condition when blood sugar level falls below the physiological limits. Classical signs appear when the glucose level of blood falls below 55mg/100ml and consists of giddiness, palpitation, sweating, hypertension, anginal pain, mental confusion, convulsion, coma leading to death. Hypoglycemia is acute condition; the episode lasts for a short time (minutes even hours), the patient either recovers (spontaneously or as a result of treatment) or dies due to convulsion-coma.

Pathogenesis. *Explanation*

- Brain, normally, depends only on glucose supplied by blood. Brain can not store glucose, hence fall of blood glucose level, below a critical level, produces signs and symptoms immediately.

- Low blood glucose level damages the brain but side by side, immediately compensatory mechanisms develops, which includes,
  1. stimulation of sympathetic
  2. release of adrenalin from adrenal medulla – both by glycogenolysis in the liver try to restore blood sugar level immediately.
  3. also release of glucagons
- However, sympathetic stimulation and Ad release, as side reactions, cause hypertension – tachycardia-anginal pain – sweating.
- If the blood glucose level remains low (despite the compensatory mechanism), convulsion – coma – death can follow.

Glucagon

Glucagon (a polypeptide) is produced by the α cells of the islets of Langerhans of pancreas. Upper part of s-intestine also produces glucagons.

Functions

The two principal target cells of glucagons are:

1. hepatocytes and
2. β cells of the islets
3. adipocytes (at high doses)

Effects on hepatocytes: major effects are:

1. promotion of hepatic glycogenolysis → blood glucose level ↑
2. Promote gluconeogenetis
3. A third effect of glucagons is ureogenesis. For gluconeogenesis, -NH_2 free portion of the amino acid is required. The –NH_2 radical is utilized as urea. Glucagon causs increased production of urea by the liver.

Glucagon on fat metabolism: Glucagon causes lipolysis and increased production of ketone bodies.

Control of Glucagon secretion

1. Blood glucose level (BGL): high BGL (200mg/100ml) inhibits glucagons secretion.
2. Sympathetic stimulation leads to glucagons secretion

   Hypoglycemia → sympathetic stimulation → glycogenolysis + glucagons secretion → correction of hypoglycemia.

3. Aminoacid level in the blood. When blood level of a.a. rises → glucagons secretion is stimulated.
4. Insulin and somatostatin inhibit glucagon secretion.

Somatostatin

Somatostatin is secreted by δ cells of the islets. It inhibits glucagons and insulin both. Somatostatin secretion is stimulated by glucose – aminoacid meals. The inhibitory action on α and β cells of the islets is achieved by probably, paracrine effect of somatostatin.

+ = stimulates
- = inhibits

Apart from the islet cells, somatostatin is secreted from: (I) brain and CNS, (II) GIT. Hypothalamic somatostatin inhibits GH release.

Pancreatic polypeptide (PPP)

F cells of the islets produce PPP which is a polypeptide hormone and structurally related to the neurotransmitter neuropeptide Y in the CNS. Fasting and hypoglycemia increases the secretion of PPP. Physiological significance of this hormone is uncertain.

Blood sugar and its regulation

Role of hormones

	Blood sugar level	Gluconeo genesis	Glyco genesis	Keto genesis
Insulin	↓	↓	+	↓
Ad/NE	↑	↑	-	↑
Glucagon	↑	↑	-	↑
Cortisol	↑	↑	+	↑
Thyroxine	↑	↑	-	↑
GH	↑	↑		↑

+ = Promotion o synthesis; - = breakdown of glycogen; ↑= increases; ↓= decrease

Fig.1. Factors stimulating /inhibiting β cells